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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	11

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/512,019	HONG ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-13,24-30,39 and 40* is/are pending in the application.

4a) Of the above claim(s) *24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *9-13,29,30 and 39* is/are rejected.

7)☐ Claim(s) *40* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 9-13, 24-30, 39 and 40 are at issue and are present for examination.

Election/Restrictions

Applicant's election without traverse of Group I, Claims 9-13, 29, 30, 39 and 40 in Paper No. 10 is acknowledged.

Claims 24-28 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 10.

Priority

Applicants statement on the first line of the specification, that "this application is a continuation-in-pat of Serial No. 08/544,643 (now U.S. Patent 5,747,298), filed October 18, 1995 and 08/642,684, filed May 3, 1996, and the entire contents of both applications are incorporated herein by reference" is acknowledged. It is further acknowledged that the instant application is actually a divisional application of 09/157, 397, (now U.S. Patent 6,165,765) filed September, 21, 1998 which is a continuation-in-pat of Serial No. 08/544,643. It is suggested that the first line of the specification be amended to reflect this information.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosure, Paper No. 7, filed 5/1/2002, is acknowledged. Those references considered have been initialed.

Specification

The disclosure is objected to because of the following informalities:

Figures 4 through 8 each contain nucleotide sequences that are encompassed by the definitions of nucleotide sequence and thus require a sequence identifier and this sequence identifier should be listed either in the figures themselves or in each description of the figure.

In the first line of the abstract applicants recite "genetical modification". It is believed that "the genetic modification" is more appropriate.

Appropriate correction is required.

Claim Objections

Claims 29, 39, 40 are objected to because of the following informalities:

Claims 29 and 39 each recite "95% homology **of** a DNA polymerase". It is believed that "95% homology **to** a DNA polymerase" would be more appropriate.

Claim 40 recites "SEQ ID:NO 3". This should be "SEQ ID NO: 3".

Claim 40 is dependent on rejected claim 39.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-13, 29, 30 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 29, 30, and 39 are indefinite in that they are unclear in that they are each drawn to a nucleotide sequence that shares not less than 95% homology to a DNA polymerase isolated from a strain of *Bacillus stearothermophilus* or *Bacillus caldotenax*, wherein said nucleotide sequence encodes a threonine, proline and leucine at positions 342-344 and a tyrosine at position 422. These recitations are unclear in that the reference sequence of 'a DNA polymerase isolated from a strain of *Bacillus stearothermophilus* or *Bacillus caldotenax"* is unclear. Further as most of those nucleotide sequences of the claimed genus will probably have a different numbering scheme with respect to the reference nucleotide sequences, reference to positions 342-344 and 422 is unclear.

Claim 9 (10-13 dependent on) is indefinite in that the recitation "and reduces selective discrimination against incorporation of fluorescent dye-labeled

dideoxynucleotide terminators ddCTP and ddATP," is unclear. It is unclear what "reduces" selective discrimination. If it is applicants intent that the "modified DNA polymerase" has a reduction in the selective discrimination against incorporation of fluorescent dye-labeled dideoxynucleotide terminators ddCTP and ddATP", it is suggested that applicants amend the claim to reflect this more clearly.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 10, 13, 29, 30 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 9, 10 and 13 are directed to all possible host cells which produce any modified DNA polymerase which during DNA sequencing effectively incorporates fluorescent dye-labeled dideoxynucleotide terminators and reduces selective discrimination against incorporation of ddCTP and ddATP, wherein the DNA polymerase in its unmodified state selectively discriminates against incorporation of fluorescent dye-labeled dideoxynucleotide terminators ddCTP and ddATP, but does not discriminate against incorporation of fluorescent dye-labeled dideoxynucleotide terminators ddTTP and ddGTP (claims 9 and 13), wherein said modified DNA

polymerase has a proofreading 3'-5' exonuclease activity during DNA sequencing of a DNA strand from a template, such that the DNA polymerase functions to excise mismatched nucleotides from the 3' terminus of the DNA strand at a faster rate than the rate at which the DNA polymerase functions to remove nucleotides matched correctly with nucleotides of the template (claim 10). Claims 29, 30 and 39 are directed to all possible nucleotide sequences encoding a DNA polymerase which has an amino acid sequence that shares not less than 95% homology of a DNA polymerase isolated from a strain of *Bacillus stearothermophilus* or *Bacillus caldotenax*, which nucleotide sequence encodes threonine, proline and leucine residues at positions 342-344 respectively, and a tyrosine residue at position 422 (claims 29 , 30, and 39).

The specification, however, only provides a single representative species of host cells comprising a nucleotide sequence and the nucleotide sequences itself, wherein the nucleotide sequence encodes the modified DNA polymerase which comprises the amino acid sequence of SEQ ID NO: 4, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these host cells and nucleotide sequences by any identifying structural characteristics or properties other than the activities recited in claims, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 9, 10 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA construct comprising a nucleotide sequence and a host cell comprising said nucleotide sequence, wherein said nucleotide sequence encodes a modified DNA polymerase which during a DNA sequencing reaction has a reduced selective discrimination against the incorporation of the fluorescent dye-labeled dideoxynucleotide terminators ddCTP and ddATP, relative to the fluorescent dye-labeled dideoxynucleotide terminators ddTTP and ddGTP, and wherein said modified DNA polymerase comprises the amino acid sequence of SEQ ID NO: 4, does not reasonably provide enablement for any nucleotide sequence and a host cell comprising said nucleotide sequence, wherein said nucleotide sequence encodes any modified DNA polymerase which during a DNA sequencing reaction has a reduced selective discrimination against the incorporation of the fluorescent dye-labeled dideoxynucleotide terminators ddCTP and ddATP, relative to the fluorescent dye-labeled dideoxynucleotide terminators ddTTP and ddGTP. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir.

1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 9, 10 and 13 are so broad as to encompass any host cell which produces any modified DNA polymerase, which during DNA sequencing effectively incorporates fluorescent dye-labeled dideoxynucleotide terminators and reduces selective discrimination against incorporation of ddCTP and ddATP, and wherein the DNA polymerase in its unmodified state selectively discriminates against incorporation of fluorescent dye-labeled dideoxynucleotide terminators ddCTP and ddATP, but does not discriminate against incorporation of fluorescent dye-labeled dideoxynucleotide terminators ddTTP and ddGTP, wherein said modified DNA polymerase has a proofreading 3'-5' exonuclease activity during DNA sequencing of a DNA strand from a template, such that the DNA polymerase functions to excise mismatched nucleotides from the 3' terminus of the DNA strand at a faster rate than the rate at which the DNA polymerase functions to remove nucleotides matched correctly with nucleotides of the template.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of host cells producing modified DNA polymerases broadly encompassed by the claims, including any host cell which produces any DNA polymerase with the specified functional limitations. The

claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the modified DNA polymerases produced by the claimed host cells. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to that modified DNA polymerase which comprises the amino acid sequence of SEQ ID NO: 4.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA polymerase with the defined functional characteristics because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the specified DNA

polymerase function; (B) the general tolerance of DNA polymerases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of any DNA polymerase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the specified DNA polymerase functions claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus having the specified DNA polymerase characteristics.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any DNA polymerase that results in the specified functional characteristics. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly,

extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
February 7, 2003